77. (Amended) The process of claim 74, wherein the nucleic acid sequence comprises at least 45 contiguous nucleotides of SEQ ID NO:7, including the guanine nucleotide at position 389 of SEQ ID NO:7.

78. (Amended) The process of claim 74, wherein the nucleic acid sequence comprises at least 50 contiguous nucleotides of SEQ ID NO:7, including the guanine nucleotide at position 389 of SEQ ID NO:7.

79. (Amended) The process of claim 74, wherein the nucleic acid sequence comprises at least 75 contiguous nucleotides of SEQ ID NO:7, including the guanine nucleotide at position 389 of SEQ ID NO:7.

80. (Amended) The process of claim 74, wherein the nucleic acid sequence comprises at least 100 contiguous nucleotides of SEQ ID NO:7, including the guanine nucleotide at position 389 of SEQ ID NO:7.

81. (Amended) The process of claim 74, wherein the nucleic acid sequence comprises the nucleotide sequence of SEQ ID NO:7, including the guanine nucleotide at position 389 of SEQ ID NO:7.

82. (Amended) The process of claim 74, wherein recombinant opioid receptor polypeptide is chimeric.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

This application is a divisional application under 37 C.F.R. § 1.53(b) of Serial Application No. 08/889,108, filed July 7, 1997. At the time of the Action, claims 44-47 and 65-82 were pending. No claims have been added and claim 75 has been cancelled herein. Claims 44, 72 and 76-82 have been amended herein, without acquiescence or prejudice. Claims 44 and

72 have been to clarify the claimed invention. Claims 76-82 have been amended to correct their dependencies after the Examiner renumbered the claims, and therefore, were not done for purposes of patentability. Therefore, claims 44-47 and 65-74 and 76-82 are currently pending. A marked version of the claims is attached hereto Appendix B. Also, for the convenience of the Examiner, Applicants have attached hereto a copy of all of the pending claims, Appendix C.

B. The 35 U.S.C. § 112, First Paragraph Rejections Are Overcome

1. The Specification adequately supports claims 44-46

The Action rejects claims 44-46 under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description. The Examiner concedes that there is an adequate written description of the mu opioid receptor of SEQ ID NOS:2, 4, 8, and 17. Claims 44-46 have been amended to recite SEQ ID NOS: 2, 4, 8, and 17 to expedite the prosecution of this case. Applicant requests that the claims as amended are adequately supported by the Specification and respectfully request that this rejection be withdrawn.

2. The Specification adequately supports claims 65-70, 73-80, and 82

The Action also rejects claims 65-70, 73-80, and 82 as lacking an adequate written description under 35 U.S.C. § 112, first paragraph. The claims are directed to screening processes for substances that interact with a mu opioid receptor involving a polypeptide encoded by a nucleic acid sequence comprising 35 contiguous nucleic acids from SEQ ID NO:7. The Examiner contends that these claims lack a written description "with regards to knowing the function of these fragments." The Examiner further alleges that "not only would these nucleic acid sequence of, for example, 35 contiguous nucleotides of SEQ ID NO:7 not encode the full length receptor, but there is no written description as to what these fragments would encode." He also states, "One of skill in the art would reasonable [sic] conclude that the disclosure fails to

provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made." Applicant respectfully traverses this rejection.

Applicant contends that some of the reasons for a rejection based on written description are not appropriate. For example, information about the "function" of fragments is completely irrelevant to the issue of written description.

As for other grounds of the rejection, Applicant notes that the claims recite SEQ ID NO:7, which is fully described. Applicant fails to understand how ***portions*** of a ***full-length sequence*** are themselves not described by the specification when the specification sets forth the entire sequence of a cDNA and the corresponding protein. Applicant makes several points additional points. First, the claims at issue are method claims; they are not composition claims. Thus, the recited element of "a recombinant opioid receptor polypeptide encoded by a nucleic acid sequence comprising at least 35 contiguous nucleotides of SEQ ID NO:7, including the guanine nucleotide at position 389 of SEQ ID NO:7" does not stand alone. The claim recites three steps and this element is just one portion of the claim. Thus, this is not a composition claim that would be considered broader than the present process claims. Second, even this element has the added limitation that a sequence have the "guanine nucleotide at position 389 of SEQ ID NO:7." Therefore, with respect to scope, these claims are not written to claim any and all recombinant opioid receptor polypeptides.

Furthermore, despite the Examiner's comments, it is clear that the specification *does* teach what the nucleic acid sequence, or portions thereof, would encode. On page 105, lines 14-19 indicates that SEQ ID NO:8 is the amino acid sequence of the cDNA provided in SEQ ID NO:7. A chart setting out the genetic code, or widely available sequencing software, allows a

person of skill in the art to determine that the amino acid sequence of SEQ ID NO:8 begins at nucleotide 238 in SEQ ID NO:7.

As for the contention that an adequate number of species are not described by the specification, Applicant contends that the specification provides ***numerous*** species because it provides an entire coding sequence from which the 35 contiguous nucleotides must be obtained.

"An applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . ." MPEP 2163 (citing *Vas-Cath, Inc. v. Marhurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). By providing the ***entire sequence of SEQ ID NO:7***, and by indicating in the specification that contiguous nucleotides of SEQ ID NO:7 were part of the claimed invention, Applicant has conveyed that he was in possession of the invention at the time the application was filed. Accordingly, Applicant respectfully requests this rejection be withdrawn.

3. Claims 44-47 and 65, 66-70, 73-80 and 82 Are Enabled

Claims 44-47 and claims 65, 66-70, 73-80 and 82 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the term "mu opioid receptor" encompasses proteins having one or more amino acid substitutions, deletions, insertions and/or additions to SEQ ID NO:2, 4, 7, 8 or 17. The Examiner further states that the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is needed. Yet further, the Examiner contends that while being enabling for the mu opioid receptor of SEQ ID NO:2, 4, 7, 8 or 17, the specification does not reasonably provide enablement for all mu opioid receptors and fragments thereof. Applicant respectfully traverses.

First, Applicant notes that the Examiner has not met his initial burden of establishing a reasonable basis to question the enablement of the invention. *See* MPEP 2164.04. Furthermore,

"it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.05 (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). Nothing has been offered to suggest the invention, as cited in the rejected claims, would *not* work as intended. As such, the burden of the PTO has not been fulfilled and Applicant respectfully requests that either this rejection be withdrawn or the examiner proffer evidence to doubt the accuracy of the specification.

Even if evidence had been offered, Applicant provides additional arguments to support his contention that the claims are fully enabled.

A patent applicant need not test all embodiments of his invention. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ 2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 USPQ 241, 218 (CCPA 1976)). Section 112 requires simply that the patent applicant provide a disclosure that sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen*, 927 F.2d at 1213.

In any event, an alleged lack of express teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform the required techniques. As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 858 F.2d, 8USPQ2d, (Fed. Cir. 1988). In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

Applicants assert that structural features are identified in the specification, for example, page 92, lines 4-28, page 93, lines 1-5, page 105, lines 26-27, page 106, lines 1-20 of the

specification, describe the regions of greatest divergence among opioid receptors and the regions that are conserved. Thus, one of skill in the art would be able to utilize this information and modify the receptors in the non-conserved regions to produce a functional receptor.

The Examiner contends that the general knowledge and level of skill in the art does not supplement the specification. Applicants submit herewith references that show that skilled artisans were using regions of various opioid receptors to construct chimeric and mutated polypeptides at the time application was filed. Note that none of these references teach or suggest the presently claimed invention. Rather they show that those of skilled in the art, at the time of the priority date of the present case, would have been able to make the claimed chimeras and mutants, if they had access to the Inventor's mu opioid receptors as disclosed in the specification. For example, Wang et al. (*Journal of Biological Chemistry* 269:25966-25969, 1994 – Appendix D) replaced the second extracellular loop of a human mu opiate receptor with a human kappa opiate receptor. Kong *et al.* (*Proceedings of the National Academy of Sciences* 91:8042-8046, 1994 – Appendix E) constructed a delta/kappa chimera and a truncated kappa receptor lacking its N-terminus. Yet further, Applicants refer the Examiner to Surratt et al. (*Journal of Biological Chemistry* 269:20548-20553, 1994 – Appendix F) which describe structural features of the mu receptor polypeptide and provides additional examples of mutations of the mu receptor. Applicants assert the evidence provided by the Applicants only needs to be convincing to one skilled in the art. *In re Brandstadter*, 484 F.2d 1395, 1406-1407, 179 USPQ 286, 294 (CCPA 1973).

Thus, Applicants assert that the specification is a guide and that one of skill in the art would be able to follow the guidelines established by the specification. Applicant refers the Examiner to *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), which states that

the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.

Yet further, the Examiner rejects the claims on the basis that "the specification is not enabled for the broad scope of that which has been claimed. . . the scope of that which is claimed is wholly indeterminate. . . a few examples do not enable the breadth of that which is claimed since undue experimentation for one of ordinary skill in the art would be required to determine which fragments are capable of interacting with a candidate compound leads to lack of enablement in producing ligand binding fragments of SEQ ID NO:7" The determination of whether a rejection is appropriate based on the scope of a claim relative to the scope of the enablement depends on two factors: "The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the invention without undue experimentation." M.P.E.P. §§ 2164.08

Applicant asserts that one skilled in the art is thus enabled to practice the invention on other mu opioid receptors of all species without undue experimentation. It is well within the knowledge of those of skill in the art to determine the target domains in which to mutate or truncate the opioid receptors. Furthermore, as discussed above, the only relevant concern with respect to the enablement of a claim should be about the truth of such an assertion; "first paragraph of 35 U.S.C. 112 requires nothing more than objective enablement; how such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

Thus, in light of the above remarks, Applicant respectfully requests withdrawal of the § 112, first paragraph, rejection.

4. Claims 44 is adequately described

Claim 44 has been rejected because the Examiner alleges that there is lack of adequate written description of the term "interact". Applicant traverses.

Applicant asserts that the specification clearly identifies and describes "interact". For example, page 71, lines 11-19 of the specification, Applicant describes:

> A candidate substance is a substance which can **interact** with or modulate, by binding or other intramolecular interaction, a mu opioid receptor polypeptide or a gene transcription regulatory polypeptide. In some instances, such a candidate substance is an agonist of the receptor and in other instances can exhibit antagonistic attributes when interacting with the receptor polypeptide. In other instances, such substances have mixed agonistic and antagonistic properties or can modulate the receptor in other ways. Alternatively, such substances can promote or inhibit transcription of a mu opioid receptor. (Emphasis added).

Thus, Applicant have adequately described all the possible interactions of the candidate substance with the mu opioid receptor and request that the rejection be withdrawn.

C. The 35 U.S.C. § 112, Second Paragraph Rejections Are Overcome

1. Claims 44-47 are definite

Claims 44-47 have been rejected as being vague and indefinite in reference to the term "mu opioid receptor". Applicant traverses.

Applicant has amended claim 44 to recite that the "mu opioid receptor" is a "recombinant mu opioid receptor polypeptide comprising the contiguous amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:8, or SEQ ID NO:17." Thus, Applicants respectfully request withdrawal of this rejection in light of the amendment to claim 44.

2. Claim 44 is definite

The Examiner contends that it is not clear from the claims or the specification to what the term "interact" in claim 44 refers. Applicant traverses.

Applicant refers the Examiner to the above 112, first paragraph, argument citing page 71 of the specification in which Applicant has clearly described the term "interact". The standard for definiteness of a claim is whether a person of skill in the art can determine the scope of the invention based on the language of the claims with "a reasonable degree of certainty." MPEP 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)). Based on the description in the Specification, one of ordinary skill in the art would have no difficulty discerning the scope of the claims. Accordingly, Applicant requests withdrawal of the 112 rejection.

3. Claim 73 is not vague

Claim 73 has been rendered vague and indefinite because part (i) and part (iv) of the claim is allegedly unclear and confusing. Applicant traverses.

Applicant asserts that the claim is clear, however, in order to advance the prosecution of the present invention, Applicant has amended the to clarify the binding ability and that the cell membrane comprises the claimed recombinant opioid receptor polypeptide. In light of this amendment, Applicant requests withdrawal of this 112 rejection.

D. The 35 U.S.C. § 102(b) Rejections Are Overcome

Claims 44-47 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hawkins *et al.* ("Hawkins") and Kennedy *et al.* ("Kennedy"). The Examiner alleges that Hawkins and Kennedy teach a process of screening a candidate substance for its ability to interact with a mu

opioid receptor by providing a mu opioid receptor polypeptide, a candidate substance and measuring the binding affinity of the ligand for the receptor. Applicant traverses.

Hawkins and Kennedy describe cell lines that are known to contain native mu opioid receptors. In the present invention, a "recombinant" mu opioid receptor is involved.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). The references do not teach a "recombinant" mu opioid receptor. Accordingly, the cited references do not anticipate claims 44-47. Applicant respectfully requests withdrawal of the rejection.

III. CONCLUSION

Claims 44-47, 65-74 and 76-82 are pending in this application. Claims 44, 72 and 76-82 have been amended without acquiescence or prejudice. Claims 44 and 72 have been to clarify the claimed invention. Claim 75 has been deleted. Claims 76-82 have been amended to correct the dependency after the Examiner renumbered the claims. Therefore, these amendments do not narrow the scope of the claims within the meaning of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 586, 56 USPQ2d 1865, 1886 (Fed. Cir. 2000).

Attached hereto is a marked-up version of the changes made to the specificationa dn claims by the current amendment. The attached appendices are captioned "Version with markings to show changes made", Appendix A and "Version with markings to show changes made", Appendix B.

The Examiner is invited to contact the undersigned attorney at 512-536-3035 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Mark B. Wilson
Reg. No. 37,259
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
Telephone: (512) 536-3081
Facsimile: (512) 536-4598

Date: April 6, 2001